CICATRIZANT HYDROCOLLOIDAL PATCH CONTAINING HYALURONIC ACID AND CHONDROITIN SULPHATE

Field of the invention

The present invention concerns a cicatrizant hydrocolloidal patch and the relative preparation process.

State of the art

Cicatrizant pharmaceutical formulations for topical use, based on hyaluronic acid or a pharmaceutical salt thereof, have been known for some time.

For instance EP 0480198 describes pharmaceutical compositions containing the sodium salt of hyaluronic acid and antiseptic substances for topical use.

However, these compositions are in hydrogel form and have the disadvantage of adding liquid to the wound when applied to it, hence making it even more difficult to eliminate the exudate from the wound.

These drawbacks are solved with the self-supporting dry transparent film described in international patent application WO 97/02845, consisting of a mixture of at least one hydrocolloid and hyaluronic acid.

This film is prepared with a process that envisages the following steps:

· preparation of a very diluted aqueous composition containing hyaluronic acid at concentrations between 0.5 and 2% in weight, and hydrocolloids at concentrations between 1% and 20% optionally in the presence of an additional solvent such as glycerol.

· casting of the composition on a support,

· exsiccation of all the liquid components of the aforesaid composition by treatment in a stove.

An anhydrous film is thus obtained in which the content of hyaluronic acid is between 2 and 98% and the remaining components to 100% are the hydrocolloids.

The complete elimination of the water, achieved by exsiccation in a stove requires extremely long heating times (in the order of several hours), with a consequent notable waste of energy. In addition, since with this type of procedure it is difficult to obtain a film of uniform thickness with a constant level of anhydricity, the industrial implementation of such a process is virtually

impracticable.

Moreover, all the hydrocolloids, with the exclusion of polyvinylpyrrolidone, tend to worsen the mechanical properties of the self-supporting film, namely its tensile strength and elongation at break. To obviate such a drawback large quantities of the expensive hyaluronic acid must be added, in most cases, more than 10% and, in some cases, in the event that sodium alginate is used as the hydrocolloid, in amounts decidedly greater than 25%. Only when polyvinylpyrrolidone is employed it is possible to obtain good mechanical properties using smaller amounts of hyaluronic acid, which in any case must be around 2.5%.

In Italian patent 1301470 a cicatrizant hydrocolloidal patch is described comprising a support layer, an intermediate layer containing an adhesive polymer, at least one hydrocolloid and hyaluronic acid or a pharmaceutical salt thereof and, finally, a protective layer.

This patch does not show sufficient cicatrizant strength even at concentrations of hyaluronic acid in the order of 2% in weight out of the weight of the adhesive layer. In fact, the cicatrizant effect does not diverge, in a statistically significant manner, from the cicatrizant activity shown by the placebo patch, not containing any active principle.

In "Effect of chondroitin sulfate preparation on wound healing and strength of the surgical scar" by M. Fialkova et al BYULLETTIN EKSPERIMENTAL' NOY BIOLOGII I MEDITSINY, Vol. 108, N°9 pp. 350-351 the results of an experiment carried out on a model of "full thickness" (300 mm^2) cutaneous wound in rats are discussed, wherein such a wound has been treated with one or two applications of 30 mg of sodium chondroitin sulphate. The reduction of the damaged surface (measuring through planimetry) was more rapid in the treated group. For instance, 8 days after the second application the residual area in the treated group was half that of the control group, and also the clinical signs connected with the lesion (edema-exudate) decreased more quickly in the treated group.

The therapeutic form considered in this article diverges from that considered in the Italian patent since the active principle is administered intramuscularly by

means of an injectable solution and at high concentrations of 10%.

Summary of the invention

The Applicant has now unexpectedly discovered a cicatrizant hydrocolloidal patch containing hyaluronic acid and chondroitin sulphate as the active principle which, even at low concentrations of both chondroitin sulphate and hyaluronic acid, when it is applied to a wound allows to attain a cicatrization speed, expressed as percentage of reduction of the wound surface in time, comparable to that of bandages available on the market for the same purposes, namely CONVATEC® or VARIHESIVE-E®, but, unlike the latter, also promotes the formation of dermis and collagen production.

The object of the present invention is therefore a cicatrizant hydrocolloidal patch comprising:

a) a support layer,

b) an adhesive layer containing an adhesive polymer, at least one hydrocolloid, hyaluronic acid or a phrmaceutical salt thereof and chondroitin sulphate or a pharmaceutical salt thereof,

c) a protective layer removable at the moment of use.

Detailed description of the invention

The patch object of the present invention preferably contains hyaluronic acid in the form of one of its pharmaceutically acceptable salts at concentrations preferably between 0.01 and 5%, in weight out of the total weight of adhesive layer (b).

The molecular weight of the hyaluronic acid is preferably between 50,000 and 1,000,000.

The chondroitin sulphate in the patch of the present invention is preferably the bisodium salt of chondroitin-4-sulphate or chondroitin sulphate A, and the concentration of said active principle is preferably between 0.01% in weight and 5%. For simplification the aforesaid salt will hereafter be defined by the term sodium chondroitin sulphate.

According to a preferred solution, the concentration of sodium hyaluronate in the patch according to the present invention is between 0,01 and 1.5%, and that of sodium chondroitin sulphate is between 0.01 and 2.5%.

According to a particularly preferred solution, the concentration of sodium hyaluronate in the patch according to the present invention is between 0.05 and 1%, and that of sodium chondroitin sulphate is between 0.05 and 1%.

In fact, it has surprisingly been found that, when such active principles have concentrations that fall within the aforesaid preferred intervals and particularly when sodium hyaluronate has a concentration of 0.2% and sodium chondroitin sulphate has a concentration of 0.3% in weight out of the total weight of adhesive layer (b), the patch of the invention shows a greater cicatrizant effect compared to that a patch of similar formulation, but containing sodium hyaluronate at a concentration of 2% and sodium chondroitin sulphate at a concentration of 3% in weight out of the total weight of the adhesive layer, and comparable to that of bandages available on the market such as VARIHESIVE®.

Preferred hydrocolloids for use in adhesive layer (b) of the patch according to the present invention are sodium carboxymethylcellulose of molecular weight of between 700 and 50,000, pectin USPL optionally mixed with saccharose, or mixtures thereof.

The concentration of said hydrocolloid is preferably between 10 and 90% in weight out of the total weight of adhesive layer (b).

According to a particularly preferred solution, a mixture of the following is used as a hydrocolloid: sodium carboxymethylcellulose, commercially available under the trade name of Blancosa® 7H4XF, sodium carboxymethylcellulose commercially available under the trade name of CEKOL®, Pectin USPL available under the trade name of GENU-PECTIN, added with saccharose (Sugar mix). This mixture of hydrocolloids is preferably present in adhesive layer (b) at concentrations of between 10 and 80%, even more preferably at concentrations of 47% in weight out of the total weight of said adhesive layer (b).

The adhesive polymer of layer (b) of the patch object of the present invention is preferably chosen between polyisobutylene of molecular weight of between 500 and 100,000, isoprene/styrene copolymer or mixtures thereof, at concentrations of between 10 and 90% in weight out of the total weight of

adhesive layer (b).

According to a particularly preferred solution a mixture of polyisobutylene having a mean molecular weight of 40,000 and commercially available under the trade name of Oppanol® B15, and of styrene/isoprene copolymer Kraton® D-1107CS is used. The concentration of said adhesive polymeric mixture in layer (b) is preferably between 10 and 80%, even more preferably of 45% in weight out of the total weight of the adhesive layer (b).

The patch according to the present invention preferably contains a plasticizer chosen in the group consisting of mineral oil optionally with traces of white naphthenic oil, commercially available under the trade name of ENERPAR® and a mixture of polyterpenic resin and petroleum hydrocarbon resin, commercially available under the trade name of WINGTAC®10, and relative mixtures of said plasticizers at concentrations of between 0.5 and 25% in weight calculated out of the total weight of said adhesive layer (b). According to a preferred solution a mixture of the aforesaid mineral oil and of the mixture of polyterpenic resin/petroleum hydrocarbon resin is used and the total concentration of said plasticizer is between 1 and 10%, and even more preferably of 8% in weight out of the total weight of the adhesive layer (b).

In the patch according to the present invention preferably the support or layer (a) is made up of polyurethane as a film or a foam, while layer (c), which is the sheet removable at the moment of use, is preferably made of silicon paper.

The patch object of the present invention is preferably produced with a process that comprises the following steps:

i) dry mixing of hyaluronic acid or a pharmaceutical salt thereof and chondroitin sulphate or a pharmaceutical salt thereof with the hydrocolloid,

ii) mixing of the powders of the previous stage with the adhesive composition and optionally a plasticizer;

iii) extrusion of the paste deriving from step (ii) at a temperature of between 40 and 90°C, preferably of 80°C, between the support layer (a) and the removable protective layer (c).

Shown below are two illustrative but non-limiting examples of composition of the hydrocolloidal patch according to the present invention.

EXAMPLE 1

Hydrocolloidal patch composed of:

1. layer (c): silicon paper = 0.82 g/total weight of the patch
2. layer (b): adhesive = 10.25g/total weight of the patch,
3. layer (a): polyurethane support film = 0.62 g/total weight of the patch.

Composition of adhesive layer (b)

Trade name	Usual name	% in weight out of the total weight of layer (b)
OPPANOL® B15	Polyisobutylene	29.24
KRATON®D-1107CS	Styrene-isoprene copolymer	15.59
BLANCOSA ® 7H4XF	Sodium carboxymethylcellulose	17.55
GENU-PECTIN	Pectin USPL	11.70
CEKOL®4000	Sodium carboxymethylcellulose	15.59
SUGARMIX®	Saccharose	1.95
WINGTAC®10	Synthetic polyterpenic resin/ petroleum hydrocarbon resin	3.90
ENERPAR ®	Mineral oil with traces of white naphthenic oil	3.90
Sodium hyaluronate		0.23
Sodium chondroitin sulphate		0.35

EXAMPLE 2

Trade name	Usual name	% in weight out of the total weight of layer (b)
OPPANOL® B15	Polyisobutylene	27.78
KRATON®D-1107CS	Styrene-isoprene copolymer	14.82
BLANCOSA ® 7H4XF	Sodium carboxymethylcellulose	16.67
GENU-PECTIN	Pectin USPL	11.11
CEKOL®4000	Sodium carboxymethylcellulose	14.82
SUGARMIX®	Saccharose	1.85
WINGTAC®10	Synthetic polyterpenic resin/ petroleum hydrocarbon resin	3.70
ENERPAR ®	Mineral oil with traces of white naphthenic oil	3.70
Sodium hyaluronate		2.22
Sodium chondroitin sulphate		3.33

After cutting, each patch was sealed in a special airtight blister pack and irradiated with γ rays (normally between 25 and 50 KGy)

1- MACROSCOPIC APPEARANCE OF THE WOUNDS AND MORPHOMETRIC ANALYSIS

METHODOLOGY

Dunkin Hartley type guinea pigs were used for this test.

A rectangular wound of 12 cm^2 (4x3) was made on one side of each guinea pig (10 guinea pigs + 1 extra per group), maintaining the panniculus carnosus.

The medication was applied to the wound each day up to day 33 (end of the experiment).

The action of the medication and the appearance of the wounds were macroscopically analyzed following a scale of criteria based on moisture, adherence to the wound, inflammatory and haemorrhagic process and level of cicatrization.

A photograph was taken every two or three removals of the medication under standard conditions in order to automatically highlight the progress of the surface of the wound with an image analyser.

The following types of medication were tested.

- group A: placebo hydrocolloidal patch
- group B: hydrocolloidal plasters of example 1
- group C: hydrocolloidal plaster of example 2
- group D: VARIHESIVE ® patch

Results

a) MACROSCOPIC APPEARANCE OF THE WOUNDS

The wounds of groups A, B, and C were moist, dark and sanguinolent for most of the time, whereas the wounds of group D were moist but not as dark as those in the other groups and also less sanguinolent. However, in the latter case some yellow liquid was observed in the wounds after day 5.

A certain tendency towards better cicatrization was observed in group B when compared to group A. In fact, the wounds in group B were smaller and had a better macroscopic aspect, since covered by a thinner scab.

b- MORPHOMETRIC ANALYSIS OF THE SURFACE OF THE WOUNDS

b-1 Surface of the skin of the different groups

Table I evolution of the mean surface of the wound in different groups (cm^2)

Day	GROUP A	GROUP B	GROUP C	GROUP D
1	13.60	13.89	13.41	12.83
5	10.26	9.58	9.59	8.87
7	9.88	8.27	9.34	6.76
11	6.73	5.45	5.41	4.92
15	5.01	3.99	4.57	3.74
19	4.27	3.21	3.82	3.10
24	3.17	2.54	3.15	2.37
28	2.87	2.30	2.82	2.32
31	2.54	1.83	2.49	2.33
33	2.48	1.72	2.38	1.72

The results reported above show that in all groups the surface of the wound was reduced of approximately 50% in the first 11 days and was reduced more slowly afterwards.

A difference in the speed of cicatrization is observed between the different groups:

- 50% cicatrization of the surface for groups B and D at 8.3 and 8 days respectively, while in groups A and C this cicatrization is obtained at 10.9 and 9.4 days respectively.
- 75% cicatrization of the surface of the skin for groups B and D at 18.6 and 18.9 days respectively, while for groups A and C this value is reached at 23.8 and 23.7days respectively.

The speed in cicatrization is better in groups B and D.

b-2- Statistical analysis

Statistical analysis of the residual surface (non-parametric Mann & Whitney test) did not show any significant difference ($p< 0.05$) between groups B and D, while cicatrization in groups A and C showed the same course.

2- HISTOLOGICAL EXAMINATION

METHODOLOGY

The experiment was stopped at day 33 and the skin of three animals was taken

for each group. After fixing with 10% formaldehyde, the samples were then denatured in alcohol solutions of increasing concentration and afterwards incorporated in paraffin.

Two pairs in a series, of approx. 5 μm thickness, were made on each sample with the aid of a HM350 microtome. The sections were dyed according to a modified trichromium technique for classic histopathological analysis and with toluidine blue to highlight metachromatic oxydic structures.

The pairs of histological samples were observed using a Polyvar microscope (Reichert) fitted with a 4, 10 and 25 objective with the possibility of adding a 1.25 lens.

RESULTS

The wounds of the animals of group A and group D give similar results from a histological point of view.

Hypervascularization and exudates consisting of red blood cells and the presence of a foamy collagen-based matrix in the deep layers of the granulation tissue, were found in both groups. However, group A was associated with a more marked hypervascularization and inflammatory component when compared to group D.

The wounds of groups B and C show similar characteristics with respect to those of groups A and D, but, in addition, in the former ones the presence of a more mature deep dermis is observed. The collagen is denser and very similar to the adjacent layer of the normal dermis. This is particularly marked for the wounds of group C.

However, this group also shows a relative superficial granulation tissue of inflammatory type with a weakening of the epidermization process when compared to the wounds of group B.

Therefore, the active principles of the patches applied to groups B and C show a twoford effect, that is:

1) improved synthesis of collagen and organization in the deep layers of the wounds of groups (B) and in particular (C),

2) a more marked superficial inflammatory component associated with these active principles in the case of the groups (C).

EXAMPLE 3

Three-layer dressings (referred to as IALUSET® HYDROCOLLOIDE) consisting of (a) a polyurethane support film layer, (b) an adhesive hydrocolloid layer (formulation H010) as specified below and (c) a DSSP release paper layer were manufactured:

(a) Polyurethane Film

Permeable, translucent polyurethane film coated on one side with a pressure sensitive adhesive (SU 692).

(b) Hydrocolloid Gum

Description: A self adhesive Hydrocolloid matrix (H010) consisting of :

Oppanol B15	29,26%
Kraton-D 1107CS	15,61%
CMC Blanosa 7H4XF	17,56%
Pectin USPL	11,71%
Cekol 4000	15,61%
Sugarmix	1,95%
Sodium hyaluronate	0,20%
Sodium chondroitin sulphate	0,30%
Wingtack 10	3,90%
Enerpar	3,90%

(c) Release Liner

Description: A white paper silicone coated on both sides (Relkote 2020).

Thickness	NLT	62um
	NMT	72um
Elongation	MD	>/- 1.0%
	CD	>/- 4.5%
Tearing	MD	>/- 300 mN
	CD	>/- 320 mN
Release	NLT	200 g/5cm
	NMT	100 g/5cm

Further features of the IALUSET® HYDROCOLLOIDE dressings bearing the H010 formulation are as follows:

Sterilized Dressing: Performance Characteristics

Thickness (gum)	NLT	0.9mm
	NMT	1.1mm
Adhesiveness	NLT	550gf
	NMT	950gf
Fluage	NMT	1,5%
PH	NLT	5,5
	NMT	6,2
Swelling Index	NLT	0.5mm
	NMT	2.0mm
Absorption	NLT	300 g/m^2
	NMT	900 g/m^2

Finished Dressing Presentation

Dressing Size & Presentation

Product Ref	Size(cm)	Qty/ub
TBD	10 X 10	10
TBD	15 X 15	10
TBD	20 X 20	5

Sterilisation, Routine Control & Validation

Product is sterilised using Gamma Irradiation, such that the product has a defined Sterility Assurance Level of > = 10^{-6}

Controls applied during sterilisation are in accordance with the requirements of ISO 11137, Sterilisation of Medical Devices - Validation & Routine Control of sterilisation by Irradiation.

Reference Protocol & Report VP114

Minimum absorbed dose 25.4 kgy

The IALUSET® HYDROCOLLOÏDE as above, manufactured by the Applicant, was then subjected to clinical testing:

In particular, IALUSET® HYDROCOLLOÏDE was tested against the following reference medical device: France : DuoDERM® E (ConvaTec), Italy : DuoDERM™ CGF (ConvaTec), Switzerland : Varihesive® E (ConvaTec).

For such comparison a multicentre, prospective, randomised, controlled clinical study on the assessment of efficacy and tolerance of the new hydrocolloid dressing containing hyaluronic acid and chondroitin sulphate (IALUSET® HYDROCOLLOÏDE, IBSA/Laboratoires GENÉVRIER) vs. the reference hydrocolloid dressing (DuoDERM® E, ConvaTec) for the treatment of leg ulcers of venous or mixed origin was conducted.

Study centres: APHP Groupe Hospitalier Charles Foix, Service de Gérontologie « l'Orbe »; Ivri-Sur Seine, France; Clinica Dermatologica, Pisa, Italy; [3]U.O. Geriatria Cucinotta, Azienda Ospedaliera Policlinico S. Orsola Malpighi, Bologna, Italy; Service de Dermatologie – HCUG, Genève, Switzerland.

Study period: November 2001 – Ongoing **Clinical phase**: III.

Objectives: To compare a new hydrocolloid dressing containing hyaluronic acid and chondroitin sulphate with a reference hydrocolloid dressing, with regard to its efficacy and tolerance in the treatment of leg ulcers of venous or mixed origin.

Methodology: Multi-centre, prospective, randomised in parallel groups, vs. reference device controlled clinical trial.

Number of subjects: A total of 120 patients (60 in each treatment group) were to be recruited. A first analysis was foreseen in the middle of the trial (approximately after the treatment of the first 60 patients) to allow the Sponsors to complete the clinical section of the dossier for the EC marking application (see also Statistical Method).

Diagnosis and criteria for inclusion: Leg ulcers of venous or mixed origin (venous-arterial).

Test product (medical device), dose and mode of administration: One 10 x 10 cm dressing was applied to the ulcer, after a careful cleaning of the wound; the posology was adjusted to the individual needs of each patient, which is to say that the hydrocolloid dressing was replaced at the moment when its hygroscopic effect (exsudate re-absorption) was finsihed; in any case each application was not left in place for more than 7 days.

Duration of treatment: Until complete healing of the ulcer or until termination of patient's participation into the study for any of the reasons foreseen by the protocol. A maximum treatment period of 6 weeks was foreseen. The patients included in this intermediate analysis were completed during a period of 8 months following the study initiation.

Reference medical device, dose and mode of administration: Patients receiving the reference medical device were treated exactly the same way as described for the test device group of treatment.

Criteria for efficacy and safety: The following efficacy criteria were recorded at entry and then at day 7, 14, 28 and 42 (completion of the trial). The primary clinical outcome criterion was the percentage of reduction of the wound area, transferred by means of tracings and analysed using a digital planimeter. The secondary clinical outcome criteria included: aspect/nature of the wound area (percentage of necrotic, fibrinous or granulation tissue), symptoms (pain, itching, by VAS), appearance of the peri-ulcerous skin (œdema, purpura, peri-ulcerous erythema, horny edges, maceration, oozing and smell) assessed by means of a semi-quantitative scale, overall treatment efficacy (judged by both physician and patient), nature and quantity of analgesics taken by the patient. The following safety parameters were assessed: overall tolerance of the treatment, judged by both the physician and the patient by means of a semi-quantitative verbal scale and the recording of side effects. Primary objective of this intermediate analysis was the evaluation of both the safety profile and the performance of the new device, as compared to the reference product, in order to apply for the EC marking.

Statistical m thods: The statistical analysis of the results was performed by an independent Institute of Biostatistics (ECOSTAT, Issy les Moulineaux, France) using S.A.S. statistical software. A first analysis was foreseen approximately after the treatment of the first 60 patients to be assured of the product's tolerability and to allow the Sponsors to complete the clinical section of the dossier for the EC mark application. It is not foreseen that the results of this analysis could stop the study and they will not be taken into account in the final analysis of the trials, which will include all the 120 patients. The protocol 00CHFI/Ial02 specified the methods which had to be used for statistical analysis. The initial characteristics of the patients at time of the inclusion were compared using Fisher exact Chi square test for yes/no variables, Mantel-Haenszel test for trend for ordinal variables, and Wilcoxon non-parametric test on the rank of the values for quantitative variables. The frequency of draw backs and adverse events was compared using Fisher exact test. These analyses were performed on all the included patients. The present report is a safety report: the efficacy results are only described, the aim being to assess that the efficacy of Ialuset® Hydrocolloïde is comparable to that of DuoDERM®. This description was performed on all available data of all the randomised patients and data. At each visit, patients with missing value were excluded. Thus this description is not an intent to treat analysis and it has not been performed on the last known values.

Summary of the results: The clinical trial nr 00CHFI/Ial02 sponsored by IBSA and Laboratoires GENÉVRIER aimed at comparing the efficacy and tolerance of a new hydrocolloidal dressing, Ialuset® Hydrocolloïde, versus a reference hydrocolloidal dressing (DuoDERM®, ConvaTec) in the treatment of leg ulcers of venous or mixed origin. The duration of the treatment was planned to be 42 days. After inclusion, 4 visits, at day 7, day 14, day 28 and day 42 were planned.

This Interim Report presents an intermediate analysis, limited to the safety of the product, which was planned in the study protocol in order to obtain the EC marking, as explained in the Statistical Method section. A total of 65 patients having completed their clinical course were included at time of the intermediate safety analysis. All the 65 included patients fulfilled the inclusion and exclusion criteria. Only 2 patients had stopped their treatment before the day 42 visit for another reason than the complete cicatrisation of the ulcer. No patient used unauthorised drugs during the clinical trial course. One patient, nr. 177 from Pisa, included in the DuoDERM® group reported an adverse effect during the clinical course. The adverse event was an infection of low severity occurring on December 13, 2001, between day 7 and day 14 visits. It was treated by Ciprofloxacine, with a good evolution. The relation to treatment was quoted as "possible". The treatment was not stopped. Another patient, nr. 217 from Pisa, included in the DuoDERM® group, died from cardiac failure at day 25. This death was considered as not related to the treatment. No patient reported any adverse effect in the Ialuset® Hydrocolloïde group. In a descriptive analysis of all the randomised patients, the efficacy of Ialuset® Hydrocolloïde appeared to be similar to that of DuoDERM®. The observed improvements in the main criteria of judgement and almost all the secondary are equal or higher in the group who received Ialuset® Hydrocolloïde than in the group who received DuoDERM®.

EFFICACY CONCLUSIONS

Even within the limits of this intermediate analysis, where only 65 out of the 120 foreseen patients were analysed, and where only a description of the efficacy results was given in order to allow for a comparison between the effects/performance of the two treatments, it can be stated that there are enough evidences to support an overall comparability of the two hydrocolloid dressings, Ialuset and DuoDERM®.

Taken all together, the efficacy parameters chosen for this study give an equal, positive impression about the capability of the new tested hydrocolloid dressing of creating and maintaining a favourable environment in the wound, in order to adequately foster the healing process.

In fact, when we consider the results obtained in term of reduction of the ulcer area (the primary efficacy parameter), we can state that patients treated with Ialuset showed a substantial decrease of the wound area during treatment. This effect was clearly present already from the first control visit, after only 7 days of therapy, and went on during the whole treatment period until the end of the study.

At day 42 (final visit), the median decrease of the wound area was 50.8 % in the group treated with Ialuset® Hydrocolloïde and 30.9 % in the group who received DuoDERM®.

The reduction of the ulcer area was more important in the Ialuset group of treatment as compared to the reference group, and this was true at each control visit, although this difference never reached the statistical significance (probably as a consequence of the small sample size).

As far as the secondary efficacy parameters, a very similar trend was observed.

The aspect/nature of the wound, as examined clinically by the Investigator at each control visits, showed a favourable evolution, simply reflecting the results registered for the primary efficacy measure.

After 42 days of treatment, the granulation process was practically completed in both groups, the mean % of granulation tissue in the wound area being 93.2 % and 89.1 % in Ialuset and DuoDERM® group, respectively (p=0.1), while the percentage of residual fibrinous tissue at the end of the treatment period was 3

times higher in DuoDERM® group (10.9 %) than in the Ialuset® Hydrocolloïde group (3.5 %).

The status of the peri-ulcerous skin was also assessed by the investigator as secondary efficacy parameter: the intensity of œdema, purpura, erythema, oozing, maceration, horny edges, and smell, as scored by means of a semi-quantitative severity scale, showed generally an almost parallel decrease in the two treatment groups during the study period. Some of these symptoms/findings were still present at the end of the 42-day treatment period, the intensity being reported as slight in most of these cases.

Similarly, the intensity of itching and pain was also scored by the patients at each control visit, by means of a 100 mm visual analogue scale.

After 42 days of treatment, a substantial decreased in VAS score for itching was recorded in both groups: the reduction being, in average, of 88.1% (s.e.m.=6.3%) in the Ialuset® Hydrocolloïde group and of 68.1% (s.e.m.=9.2) in the group who received DuoDERM®: this difference was statistically significant (p=0.05, between groups).

As far as pain is concerned, the decrease in pain scores was also more pronounced in the Ialuset group of treatment as compared to DuoDERM® group, a statistically significant difference was found between the two groups only on day 28: at this visit, the average VAS for pain decreased of 79.4% (s.e.m.=5.8 %) in the Ialuset® Hydrocolloïde group and of 54.1 % (s.e.m.= 10.1) in the group who received DuoDERM® (p=0.01, between groups).

From a quarter to a third of patients took analgesics, between two subsequent visits during the trial, for the control of pain. No significant difference was found between the two groups in the consumption of analgesics.

Consistently, at the end of the study, both patients and Investigators judged the overall efficacy of the treatments as good/very good in 80 % of cases in the Ialuset group and in 78 % of cases in the DuoDERM® group.

It is also worth to mention that no significant difference between the two treatment groups was observed (p=0.7) as far as the total amount of hydrocolloid dressings used throughout the 6-week study period.